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Design, Physicochemical, Pharmacokinetic, Drug Likeness, and In-Silico Prediction of Toxicity, Adverse Effects and Biological Activity of Fulvic Acid and Humic Acid as Potent Anti-Diabetic Agents

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ABSTRACT

This study explores the potential of fulvic acid and humic acid derivatives as anti-diabetic agents through computational methods. Diabetes, a chronic metabolic disorder characterized by high blood sugar levels, affects millions globally. This research investigates the use of derivatives of fulvic acid and humic acid, compounds found in Shilajit, as potential treatments by overcoming the insulin resistance developed in the body in Type-2 Diabetes. The study involves in-silico docking simulations to evaluate the interaction of these derivatives with the Extracellular Signal-regulated Kinase 2 (ERK2) receptor, a key target in diabetes therapy. The analysis includes predicting physicochemical properties, pharmacokinetics, drug-likeness, toxicity, and adverse effects of the derivatives. Results indicate that several fulvic acid and humic acid derivatives exhibit strong binding affinities to the ERK2 receptor. The computational analysis suggests that these derivatives possess favourable pharmacokinetic properties, indicating good oral bioavailability and absorption. Furthermore, toxicity predictions suggest that these compounds may have a relatively low risk of adverse effects. In conclusion, this in-silico study identifies promising fulvic acid and humic acid derivatives as potential anti-diabetic agents. The findings support further research and development of these compounds for diabetes treatment.

Keywords: *Fulvic Acid, Humic Acid, anti-diabetic, Insulin Resistance, In-Silico.*

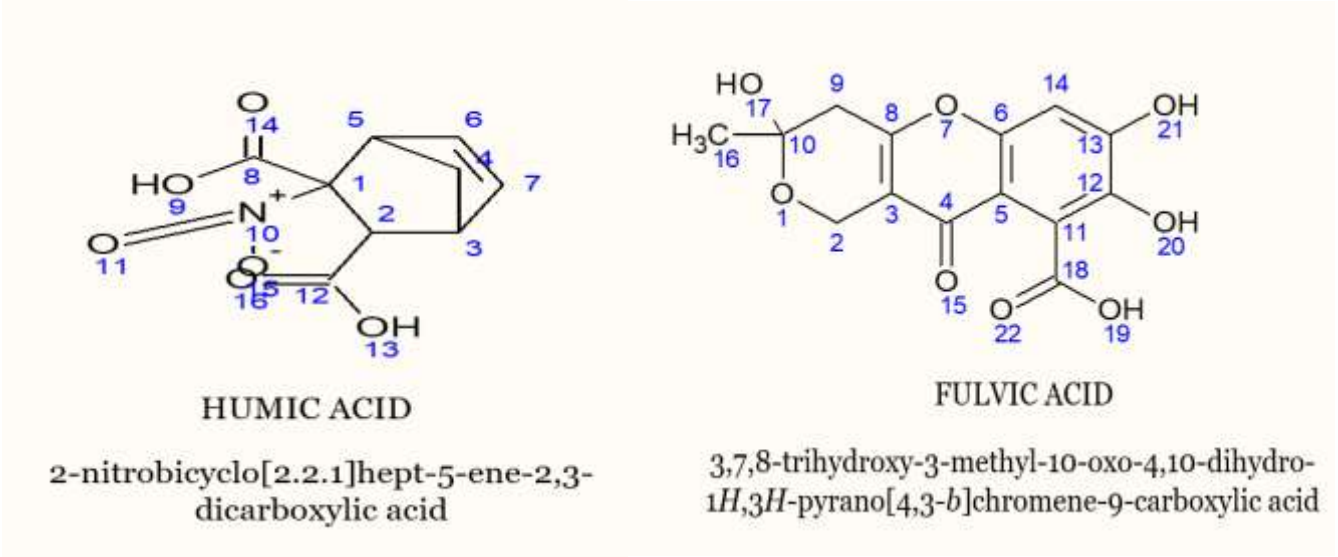
1. INTRODUCTION

Diabetes is a long-term metabolic disease that impairs the body's capacity to control blood sugar levels. If left untreated, diabetes can cause a number of dangerous health issues. In diabetics, insulin, a hormone necessary for the uptake of glucose into cells, is either insufficient or less effective (insulin resistance), which raises blood sugar levels and increases the risk of kidney failure, cardiovascular disease, and nerve damage. Over 537 million persons worldwide have diabetes as of 2024, and estimates indicate the figure could increase to 783 million by 2045, according to WHO and IDF.

The usage of derivatives of fulvic acid and humic acid as an anti-diabetic medication is investigated in this study. Shilajit, also known as Asphaltum punjabium, is a blackish-brown powder or resin-like substance that naturally oozes from rocks in high mountain regions. It contains naturally occurring heterocyclic compounds such as fulvic acid and humic acid. This substance is commonly found in the Himalayas, the Pamir Mountains, Afghanistan, the Karakoram range, Gilgit-Baltistan in Pakistan, as well as in Nepal, Bhutan, the Caucasus Mountains in Russia, the Altai region, Central Asia, Iran, and Mongolia. [3] [4] Shilajit was utilized in folk and non-traditional (alternative) medicine by Eastern peoples (Ayurveda, Chinese, Tibetan). Although shilajit is marketed as a dry extract and as a dietary supplement, there is little proof that it improves human health.

This study uses in-silico docking simulation to test the drugs and their derivatives for action on the common receptor targeted in diabetes treatment. Derivatives of fulvic acid and humic acid have demonstrated very good docking affinity with the

enzymes after being docked in the receptor Extracellular Signal-regulated Kinase 2 (ERK2). These molecules also demonstrated biological activity of the above derivatives as a strong anti-diabetic agent, as well as in-silico prediction of toxicity and adverse effects.



2. MATERIAL AND METHODS

Potential anti-diabetic compounds

The chemicals that were analysed—humic acid and fulvic acid—found in Asphaltum punjabium may have anti-diabetic properties.

Ligand Data

The ACD ChemSketch software draws all the ligands, including derivatives of humic and fulvic acids. ACD ChemSketch transformed the structures files into the necessary format.

Data on protein targets

The RCSB database (http://www.rcsb.org/pdb) provided the X-ray crystal structure information for the receptor Extracellular Signal-regulated Kinase 2 (ERK2). Following a careful review of the literature, the protein structure was chosen.

Physicochemical, Pharmacokinetics and Drug-likeness prediction

The Swiss Institute of Bioinformatics created the free online tool Swiss ADME, which is accessible at http://www.swissadme.ch and performs physicochemical, pharmacokinetic, and drug-likeness prediction. A portion of the screening procedure involves derivatives having a high binding energy score in molecular docking. Open Babel version 2.3 was used to determine common physicochemical values such as polar surface area (PSA), atom counts, molecular weight (MW), and molecular refractivity (MR). The following pharmacokinetic characteristics were anticipated: GI absorption, BBB penetration, P-gp substrate, hepatic enzymes, and log Kp (permeability coefficient). The Rule of Five (RO5) criteria put out by Lipinski (2001), Ghose (1999), Veber (2002), Egan (2000), and Muegge (2001) were used to conduct the assessment. Based on variables like total charge, topological polar surface area (TPSA), and Lipinski filter violations, the Abbott Bioavailability Score was developed to predict the probability that a chemical would have at least 10% oral bioavailability.

Toxicity Prediction

Protox 3.0, a free online tool created by the Institute of Pharmacology and Structural Biology (IPBS) and the Université de Strasbourg, is used to forecast toxicity. It may be found at https://tox.charite.de/protox3/. In addition to toxicity end points including carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity, BBB-barrier, ecotoxicity, clinical toxicity, and nutritional toxicity, predictions were made for organ toxicity, including hepatotoxicity, neurotoxicity, nephrotoxicity, respiratory toxicity, and cardiotoxicity.

Adverse Drug Reactions Prediction

The ADVER-Pred is a free online tool which can be found at https://www.way2drug.com/adverpred/, predicts adverse drug reactions. Hepatotoxicity, cardiac failure, arrhythmia, myocardial infraction, and nephrotoxicity were among the adverse medication reactions that were anticipated.

Molecular Docking and Visualization

Ligand Preparation

Open Babel was used to optimize all ligand structures (version X.X, https://openbabel.org). The Merck Molecular Force Field (MMFF94), as implemented in Open Babel, was used to minimize energy. For further analysis or docking experiments, the completely optimized 3D structures—free of symmetry constraints—were exported and stored in SDF format.

Docking Simulation

"Biovia Discovery Studio (Dassault Systemes, https://www.3ds.com/) was used to prepare the proteins. In order to add missing hydrogens, give ionizable residues the proper protonation states, and minimize energy, the protein structure was imported in PDB format and processed. The literature on docking simulations was used to determine the active location.

PyRx (https://pyrx.sourceforge.io/), which makes use of the AutoDock Vina docking engine, was used for ligand synthesis and docking. Ligand structures were prepared by converting them into the proper file format (such as PDBQT) for docking and optimizing their 3D shape. The target protein's discovered active site was the focus of docking simulations. The docking scores derived from the Biased Probability Monte Carlo (BPMC) approach were used to predict the binding affinity of the ligand-protein complexes.

The most advantageous ligand-protein interactions and possible binding modalities were determined by analyzing the docking results.

Visualization

Biovia Discovery Studio 2024 is used to visualize the Ligand-Protein interaction and capture 3D photos of it.

3. RESULTS

ANALOGUES OF FULVIC ACID

MOLECULE	SMILES	IUPAC NAME
E15	"NC(Cc2cnc1ccccc12)C(=O)c5c4OC=3CC(O)(C)OCC=3C(=O)c4c(C(=O)O)c(O)c5O"	"6-(2-amino-3-(1H-indol-3-yl)propanoyl)-3,7,8-trihydroxy-3-methyl-10-oxo-1,3,4,10-tetrahydropyrano[4,3-b]chromene-9-carboxylic acid"
C2	"FC(F)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"6-(difluoromethyl)-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid"
D23	"CC(C)C(C)(C)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"6-(2,3-dimethylbutan-2-yl)-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydropyrano[4,3-b]chromene-9-carboxylic acid"
D15	"CC(C)(CC)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"3,7,8-trihydroxy-3-methyl-6-(2-methylbutan-2-yl)-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid"
E5	"NC(Cc1cncn1)C(=O)c4c3OC=2CC(O)(C)OCC=2C(=O)c3c(C(=O)O)c(O)c4O"	"6-(2-amino-3-(1H-imidazol-4-yl)propanoyl)-3,7,8-trihydroxy-3-methyl-10-oxo-1,3,4,10-tetrahydropyrano[4,3-b]chromene-9-carboxylic acid"
J1	"NS(=O)(=O)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"3,7,8-trihydroxy-3-methyl-10-oxo-6-sulfamoyl-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid"
N1	"NC(=O)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"6-carbamoyl-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-

		b]chromene-9-carboxylic acid”
C3	“FC(F)(F)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“3,7,8-trihydroxy-3-methyl-10-oxo-6-(trifluoromethyl)-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
D4	“CC(C)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“3,7,8-trihydroxy-3-methyl-10-oxo-6-(propan-2-yl)-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
D8	“CC(C)(C)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“6-tert-butyl-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
D14	“CC(C)(C)Cc3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“6-(2,2-dimethylpropyl)-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
E3	“NC(Cc1ccccc1)C(=O)c4c3OC=2CC(O)(C)OCC=2C(=O)c3c(C(=O)O)c(O)c4O”	“6-(3,3-dimethylbutan-2-yl)-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydropyrano[4,3-b]chromene-9-carboxylic acid”
E6	“O=C(O)c4c2c(OC=1CC(O)(C)OCC=1C2=O)c(C(=O)C3CCCN3)c(O)c4O”	“3,7,8-trihydroxy-3-methyl-10-oxo-6-(pyrrolidin-2-ylcarbonyl)-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
E10	“O=C(O)CC(N)C(=O)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“6-(2-amino-3-carboxypropanoyl)-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
I1	“O=C(O)c3c2c(OC=1CC(O)(C)OCC=1C2=O)c(C#N)c(O)c3O”	“6-cyano-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
L2	“FC(=O)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“6-(fluorocarbonyl)-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
C5	“ClC(Cl)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“6-(dichloromethyl)-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
C6	“ClC(Cl)(Cl)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“3,7,8-trihydroxy-3-methyl-10-oxo-6-(trichloromethyl)-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
D5	“O=C(O)c3c2c(OC=1CC(O)(C)OCC=1C2=O)c(CCCC)c(O)c3O”	“6-butyl-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
E18	“Oc1ccc(cc1)CC(N)C(=O)c4c3OC=2CC(O)(C)OCC=2C(=O)c3c(C(=O)O)c(O)c4O”	“6-(2-amino-3-(4-hydroxyphenyl)propanoyl)-3,7,8-trihydroxy-3-methyl-10-oxo-1,3,4,10-tetrahydropyrano[4,3-b]chromene-9-carboxylic acid”
G1	“O=C(OC)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“3,7,8-trihydroxy-6-(methoxycarbonyl)-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid”
G4	“CC(C)OC(=O)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O”	“3,7,8-trihydroxy-3-methyl-10-oxo-6-[(propan-2-yloxy)carbonyl]-4,10-dihydro-1H,3H-

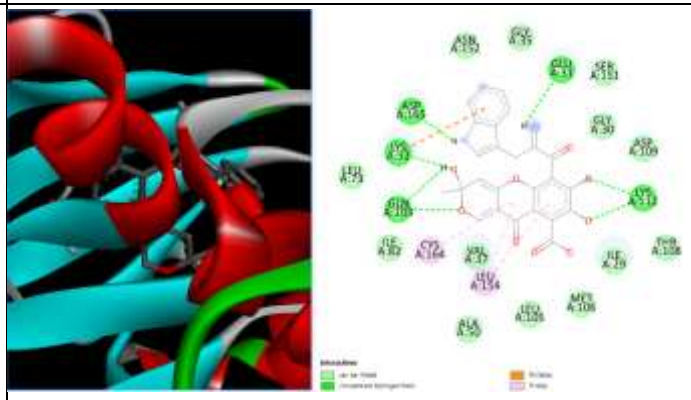
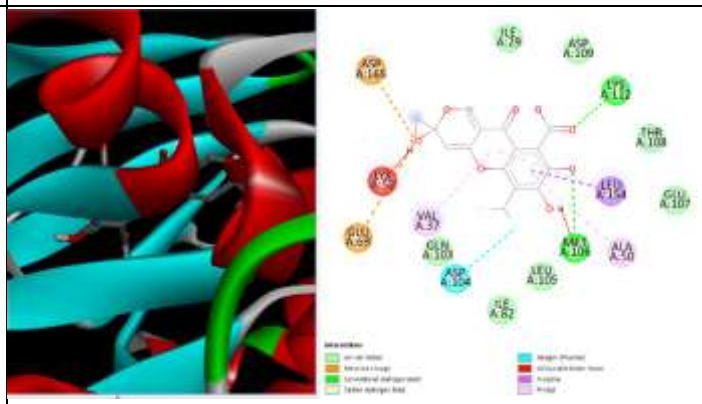
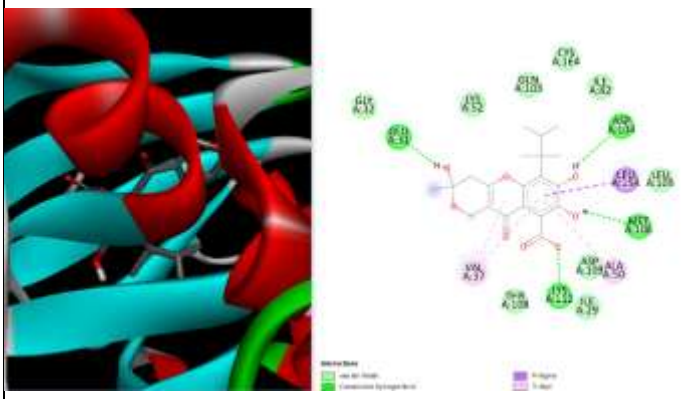
		pyrano[4,3-b]chromene-9-carboxylic acid"
J2	"ClS(=O)(=O)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"6-(chlorosulfonyl)-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid"
K1	"CC(=O)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"6-acetyl-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid"
K2	"CCC(=O)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"3,7,8-trihydroxy-3-methyl-10-oxo-6-propanoyl-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid"
L1	"ClC(=O)c3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"6-(chlorocarbonyl)-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid"
N4	"N=C(N)Nc3c2OC=1CC(O)(C)OCC=1C(=O)c2c(C(=O)O)c(O)c3O"	"6-carbamimidamido-3,7,8-trihydroxy-3-methyl-10-oxo-4,10-dihydro-1H,3H-pyrano[4,3-b]chromene-9-carboxylic acid"

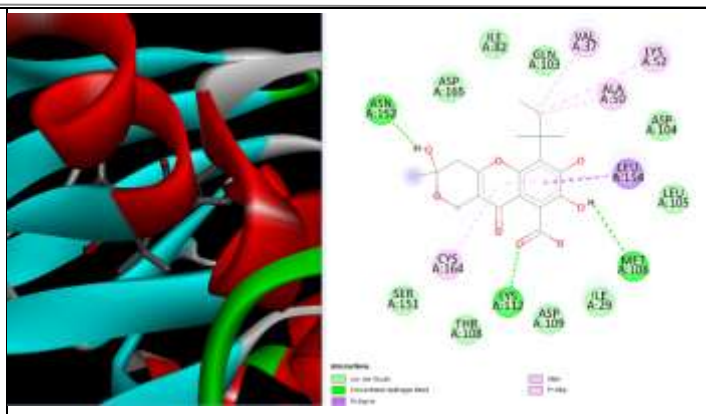
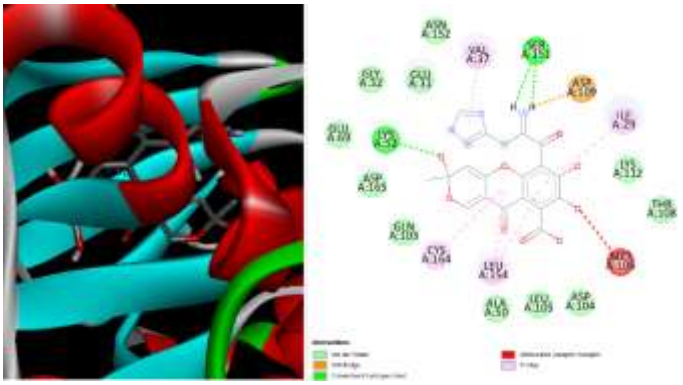
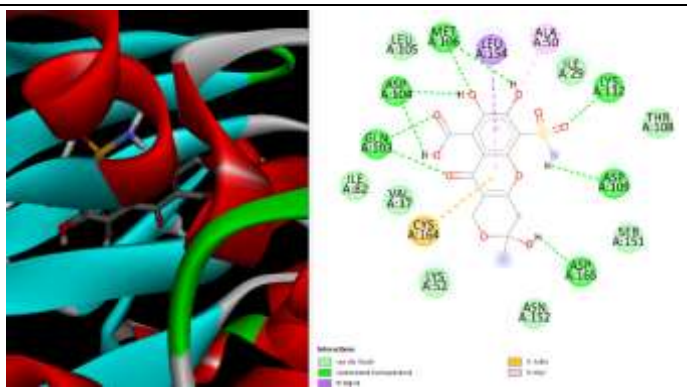
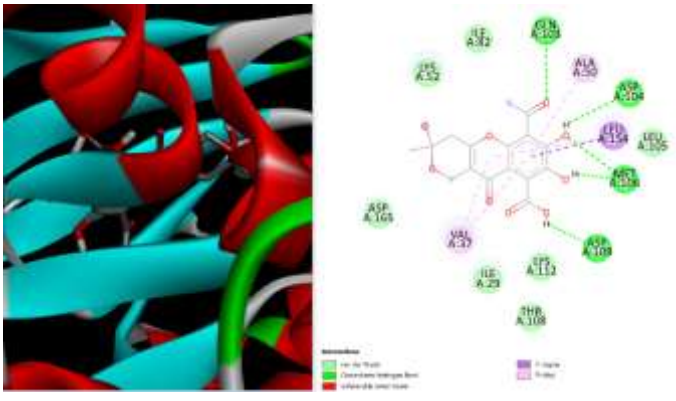
ANALOGUES OF HUMIC ACID

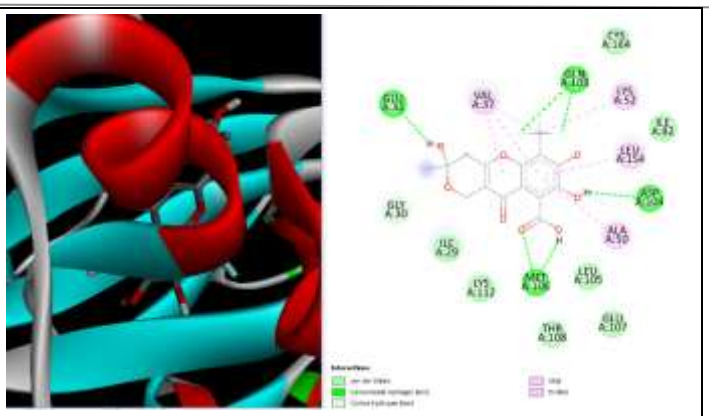
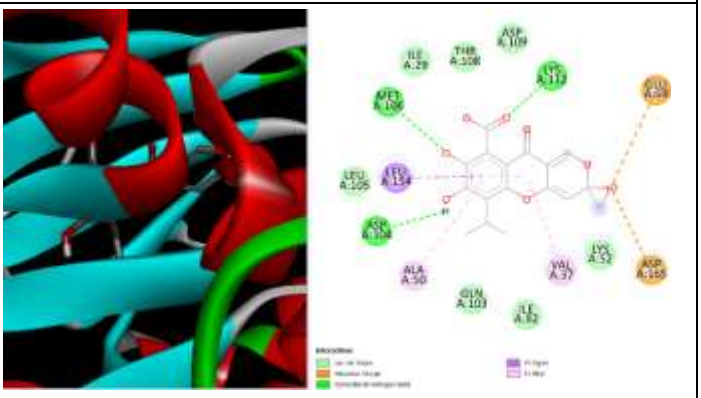
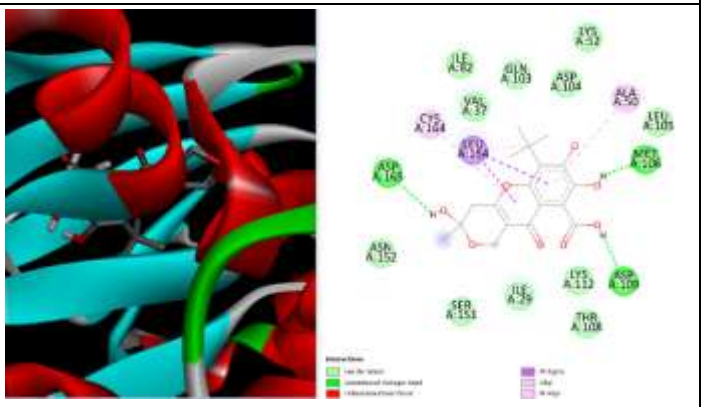
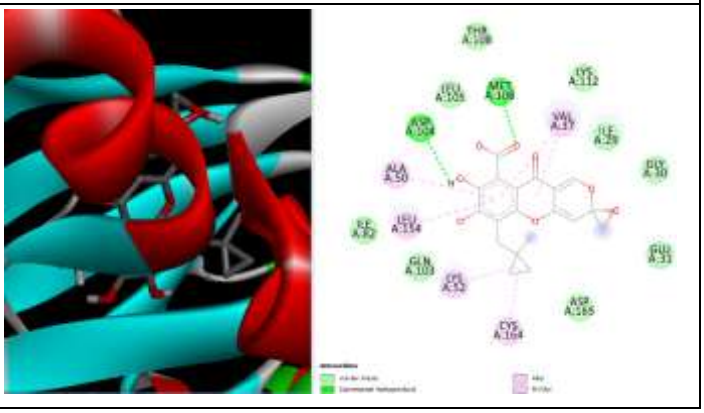
MOLECULE	SMILES	IUPAC NAME
E15	"[O-][N+](=O)C2(C(=O)O)C1C=C(C(C1)C2C(=O)O)C(=O)C(N)Cc4cnc3ccccc34"	"5-[2-amino-3-(1H-indol-3-yl)propanoyl]-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
A1	"OC(=O)C2(C1C=C(F)C(C1)C2C(=O)O)[N+]([O-])=O"	"5-fluoro-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
A4	"OC(=O)C2(C1C=C(I)C(C1)C2C(=O)O)[N+]([O-])=O"	"5-iodo-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
C3	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(F)(F)F)[N+]([O-])=O"	"2-nitro-5-(trifluoromethyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
D19	"OC(=O)C2(C1C=C(CCCC(C)C)C(C1)C2C(=O)O)[N+]([O-])=O"	"5-(4-methylpentyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
D23	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(C)(C)C(C)C)[N+]([O-])=O"	"5-(2,3-dimethylbutan-2-yl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
E4	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(=O)C(N)CCCNC(=N)N)[N+]([O-])=O"	"5-(2-amino-5-carbamimidamidopentanoyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
E10	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(=O)C(N)CC(=O)O)[N+]([O-])=O"	"5-(2-amino-3-carboxypropanoyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
E16	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(=O)C(N)CCC(N)=O)[N+]([O-])=O"	"5-(2,5-diamino-5-oxopentanoyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"

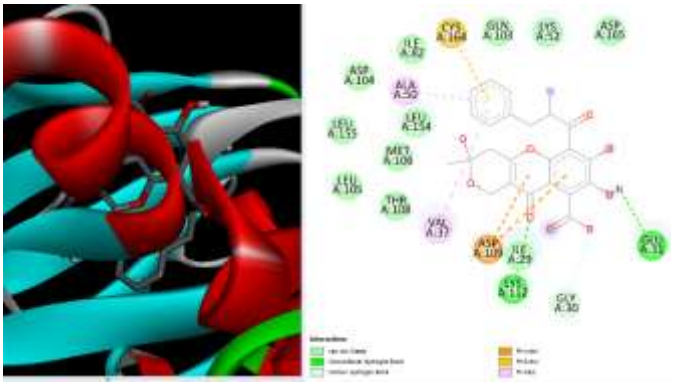
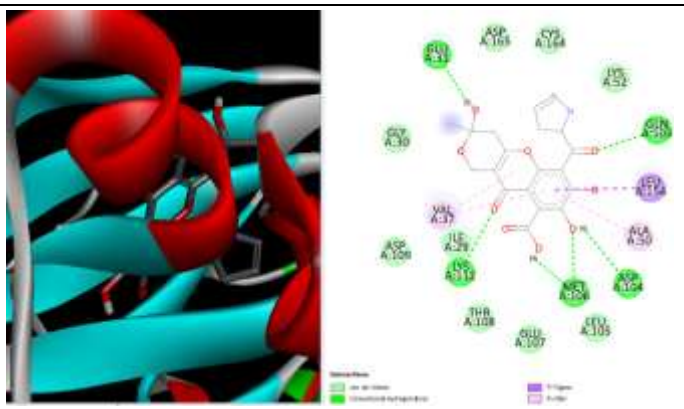
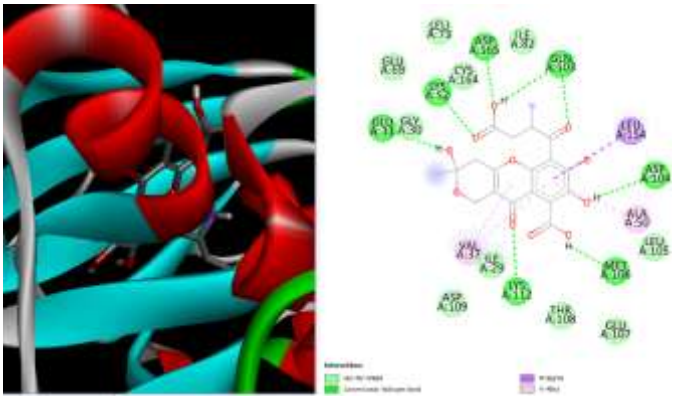
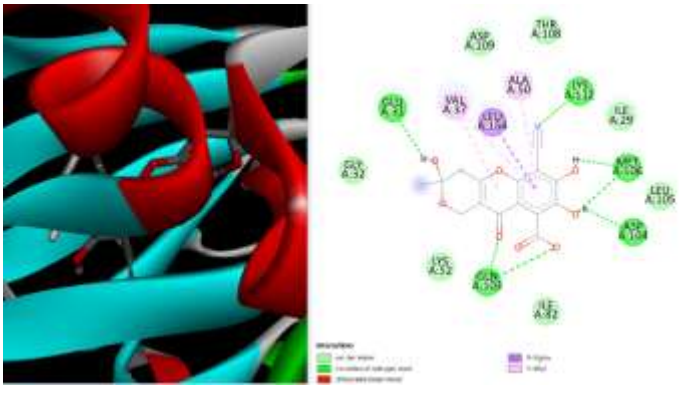
E18	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(=O)C(N)Cc3ccc(O)cc3)[N+]([O-])=O"	"5-[2-amino-3-(4-hydroxyphenyl)propanoyl]-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
I8	"OC(=O)C2(C1C=C(NO)C(C1)C2C(=O)O)[N+]([O-])=O"	"5-(hydroxyamino)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
A0	"C1C2C=CC1C(C2C(=O)O)(C(=O)O)[N+](=O)[O-]"	"2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
C11	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(I)I)[N+]([O-])=O"	"5-(diiodomethyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
C12	"c1C2C=CC1C(C2C(=O)O)(C(=O)O)[N+](=O)[O-]"	"2-nitro-5-(triiodomethyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
E3	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(=O)C(N)Cc3ccccc3)[N+]([O-])=O"	"5-(2-amino-3-phenylpropanoyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
E5	"NC(Cc1cncn1)C(=O)C3=CC2CC3C(C(=O)O)C2([N+]([O-])=O)C(=O)O"	"5-[2-amino-3-(1H-imidazol-5-yl)propanoyl]-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
E8	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(=O)C(N)C(C)CC)[N+]([O-])=O"	"5-(2-amino-3-methylpentanoyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
E19	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)C(=O)C(N)CCC(=O)O)[N+]([O-])=O"	"5-(2-amino-4-carboxybutanoyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
I6	"OC(=O)C2(C1C=C(C(C1)C2C(=O)O)S(N)(=O)=O)[N+]([O-])=O"	"2-nitro-5-sulfamoylbicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
B3	"OC(=O)C2(C1C=C(OBr)C(C1)C2C(=O)O)[N+]([O-])=O"	"5-(bromooxy)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
D6	"OC(=O)C2(C1C=C(CC(C)C)C(C1)C2C(=O)O)[N+]([O-])=O"	"5-(2-methylpropyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"
D14	"OC(=O)C2(C1C=C(CC(C)(C)C)C(C1)C2C(=O)O)[N+]([O-])=O"	"5-(2,2-dimethylpropyl)-2-nitrobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid"

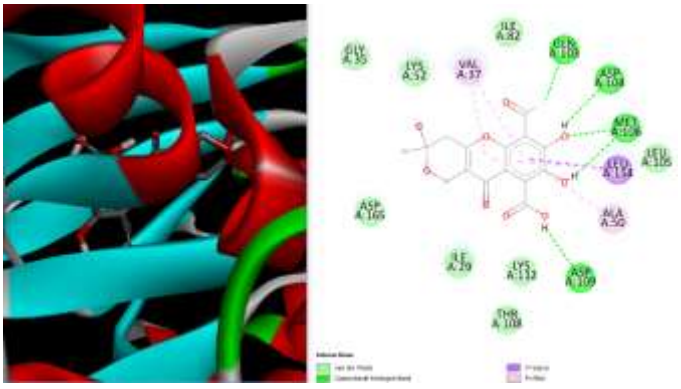
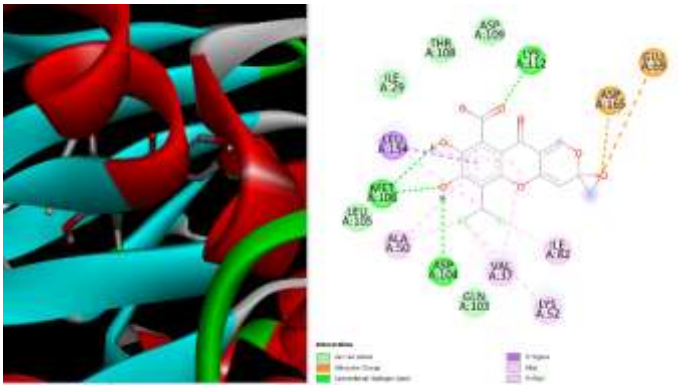
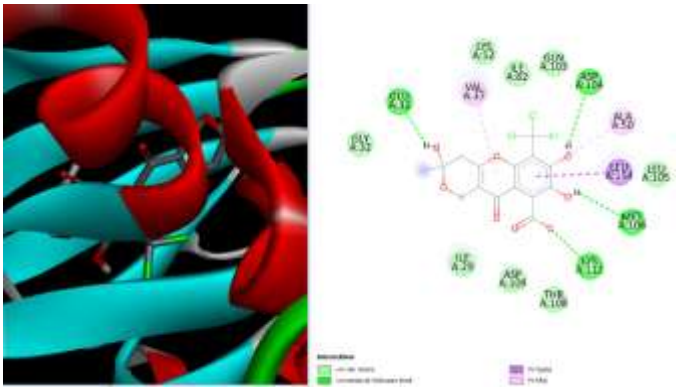
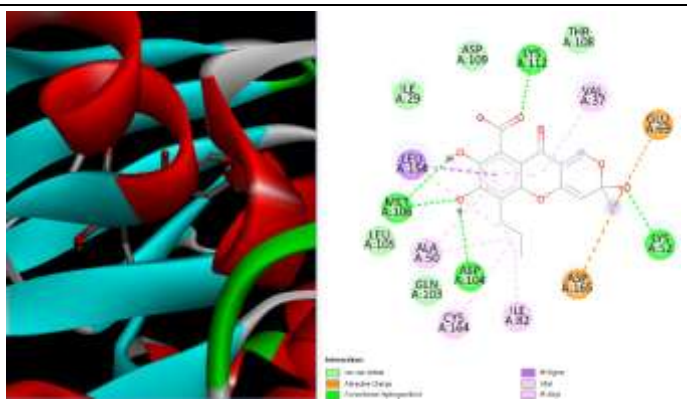
Docking Results of Fulvic Acid

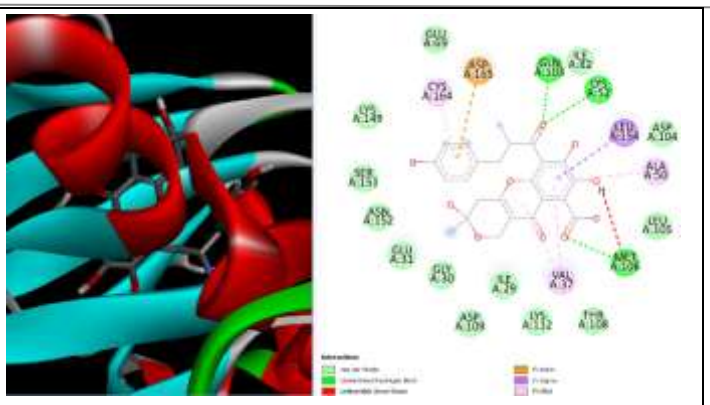
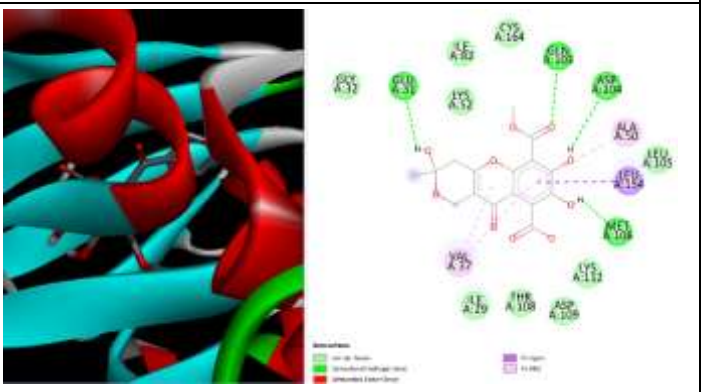
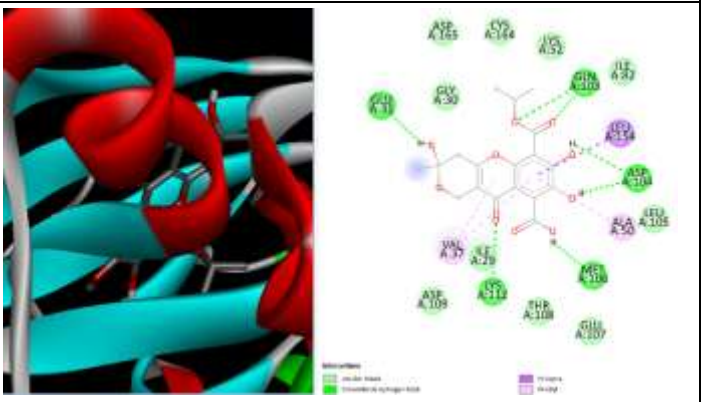
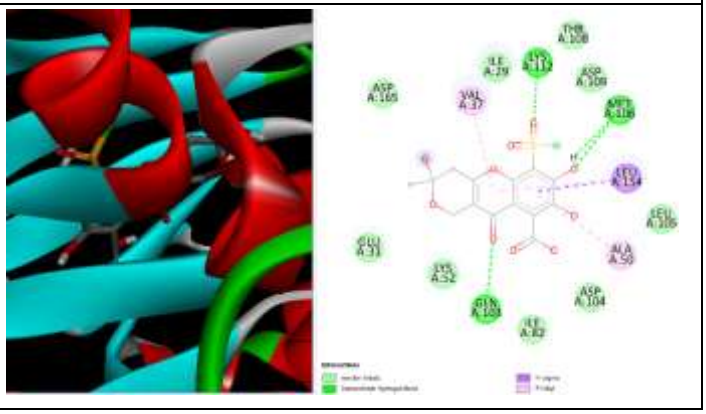
LIGAND	BINDING AFFINITY	VISUALIZATION
E15	-9.4	
C2	-8.8	
D23	-8.8	

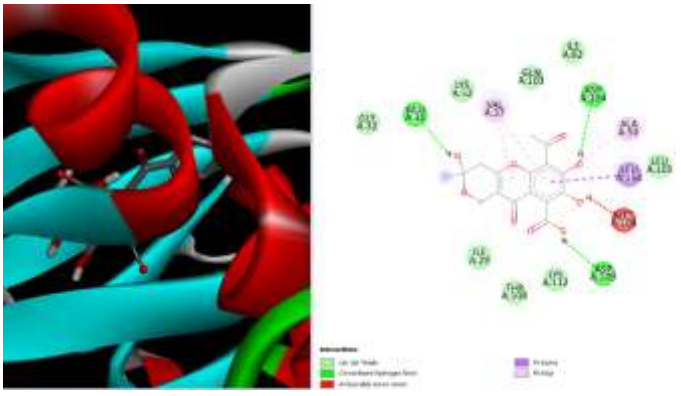
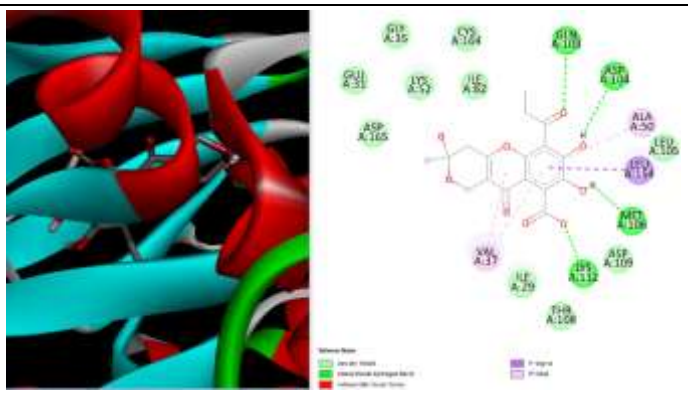
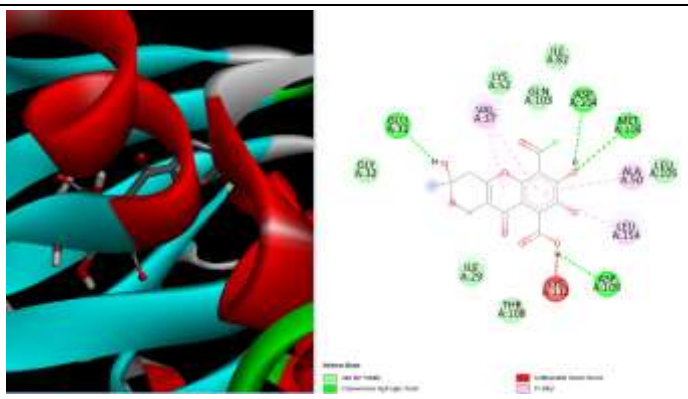
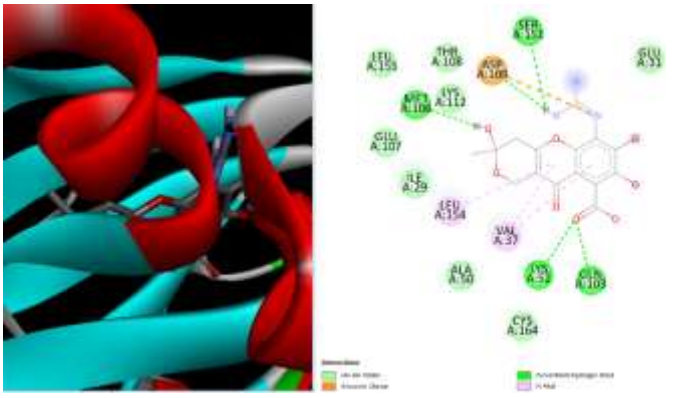
D15	-8.7	
E5	-8.7	
J1	-8.7	
N1	-8.7	

C3	-8.6	
D4	-8.6	
D8	-8.6	
D14	-8.6	

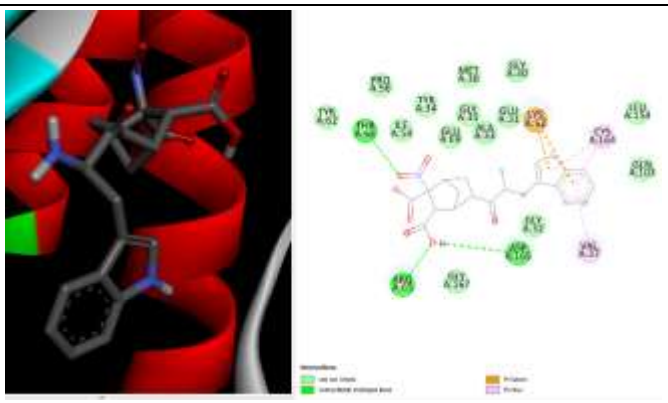
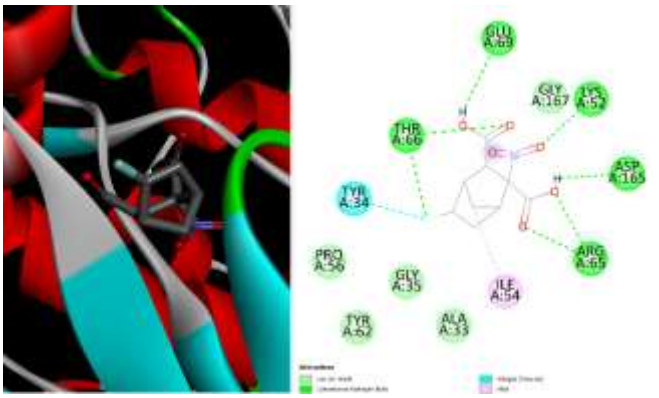
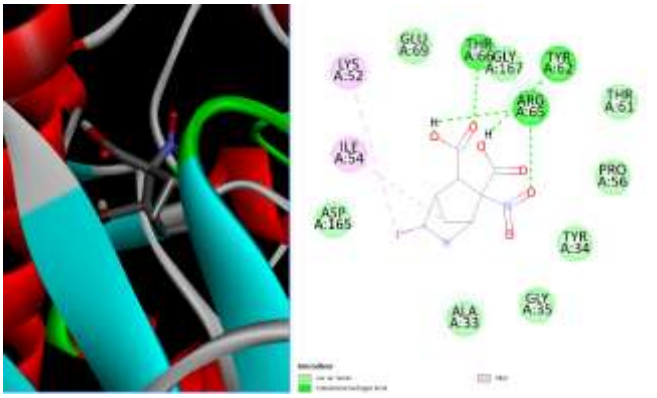
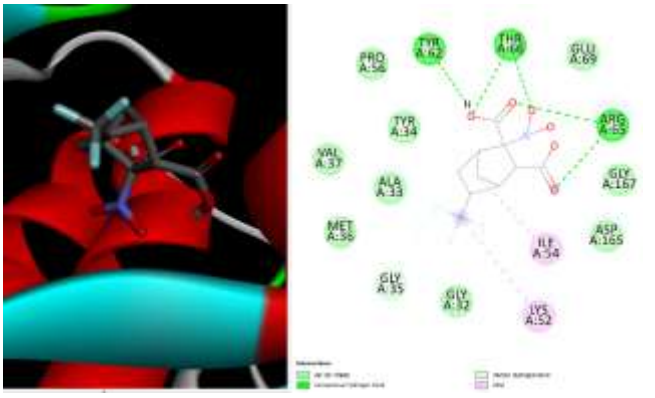
E3	-8.6	
E6	-8.6	
E10	-8.6	
I1	-8.6	

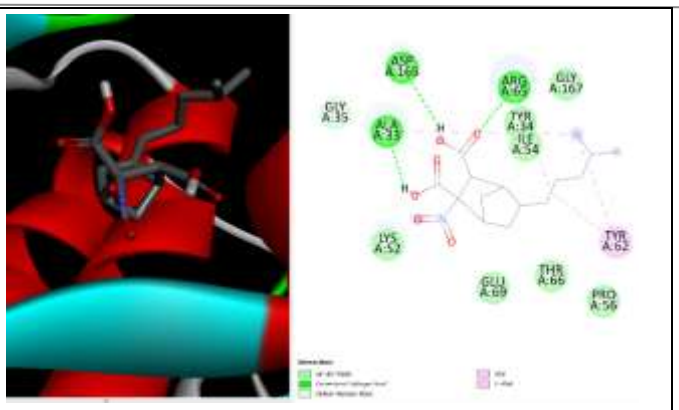
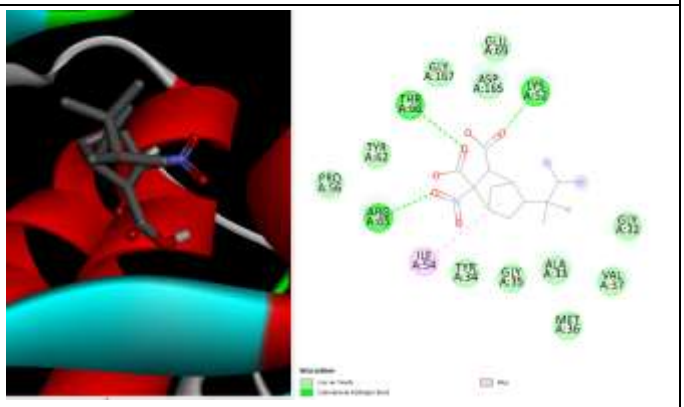
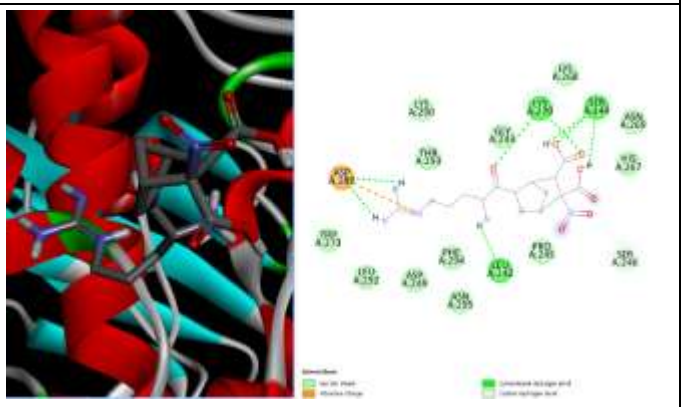
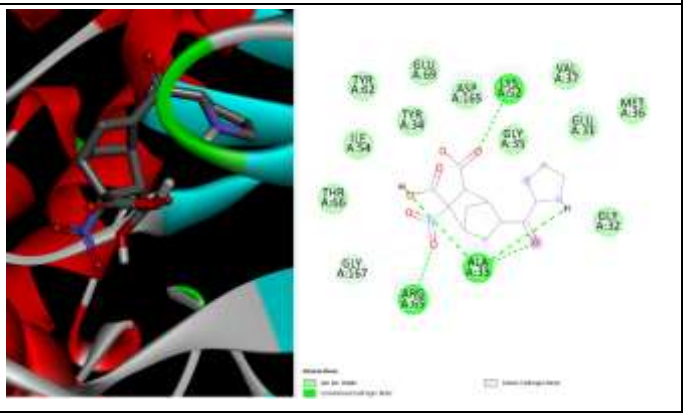
L2	-8.6	
C5	-8.5	
C6	-8.5	
D5	-8.5	

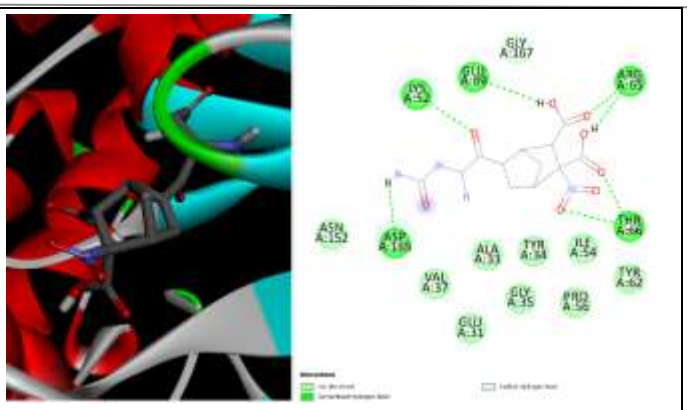
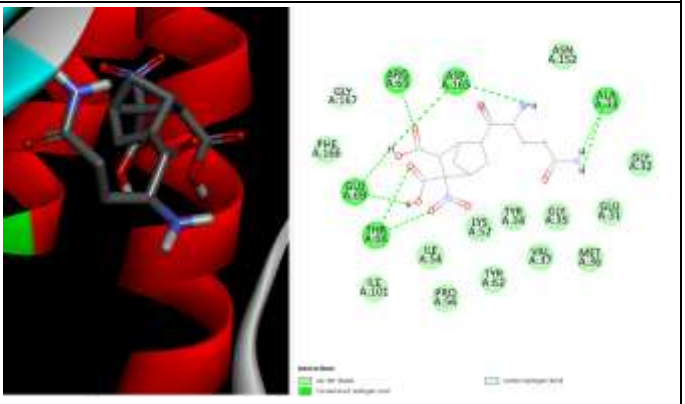
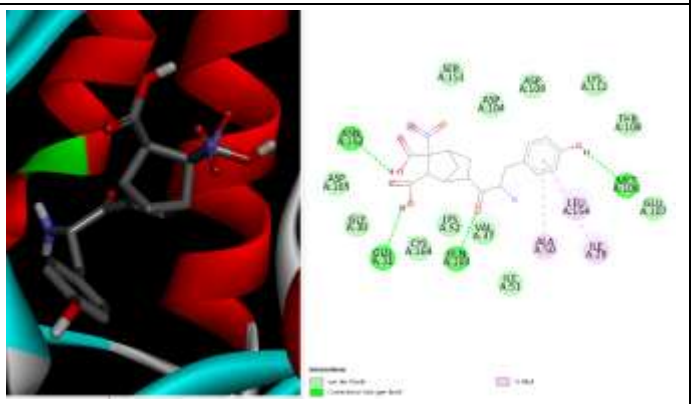
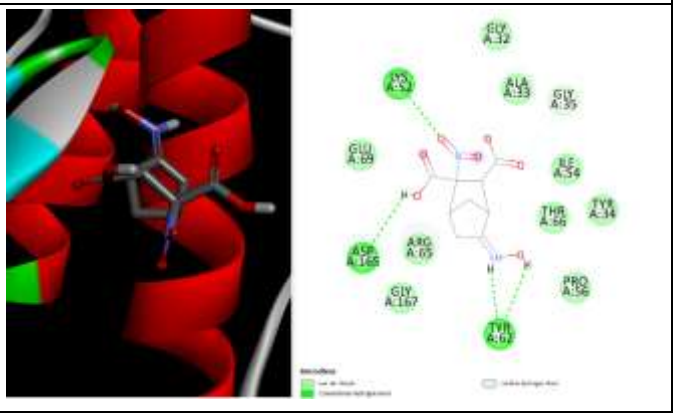
E18	-8.5	
G1	-8.5	
G4	-8.5	
J2	-8.5	

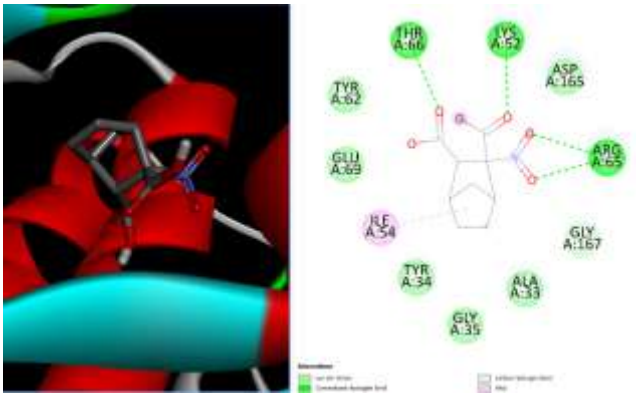
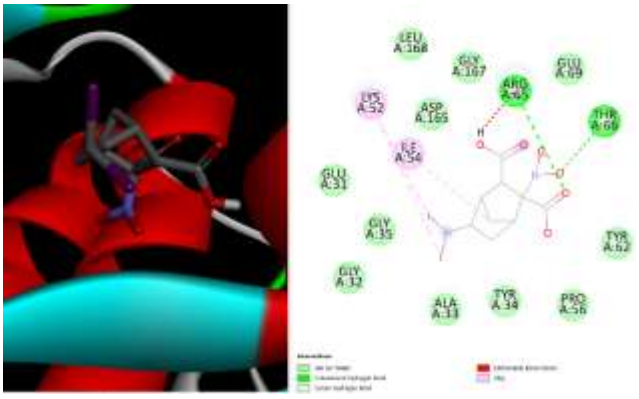
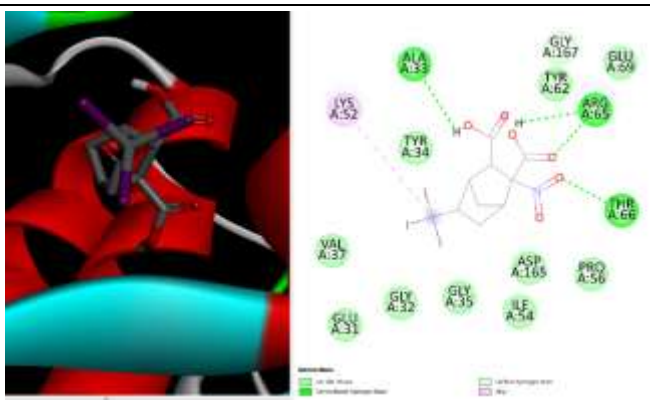
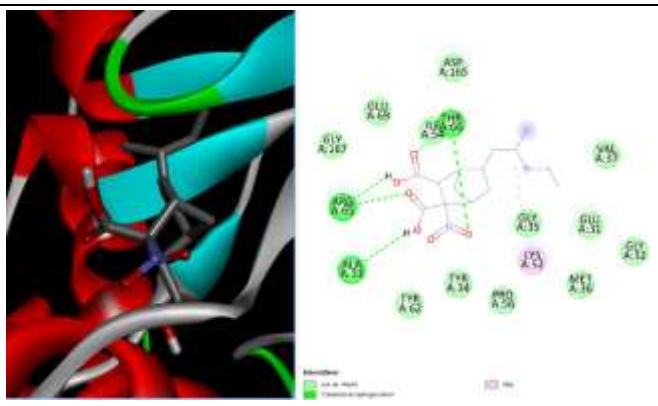
K1	-8.5	
K2	-8.5	
L1	-8.5	
N4	-8.5	

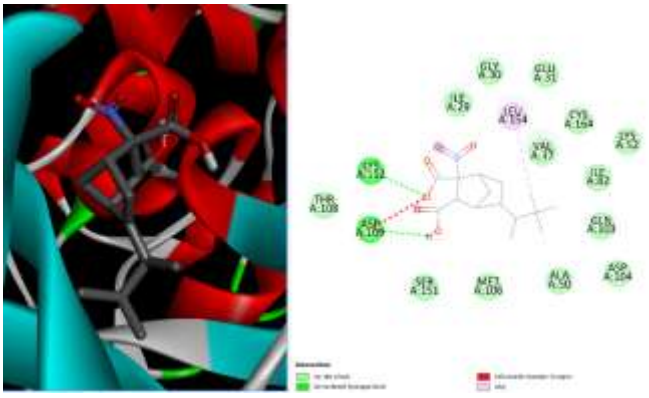
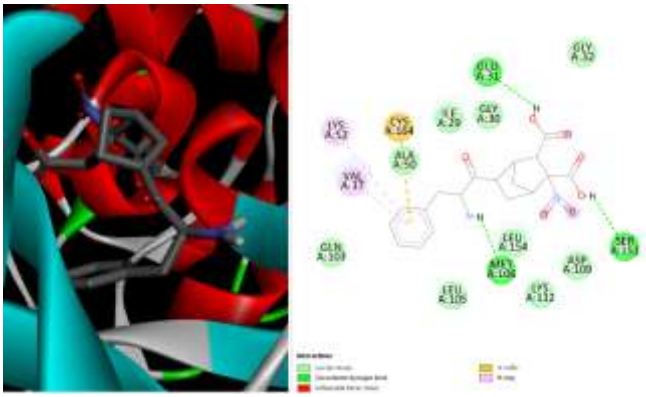
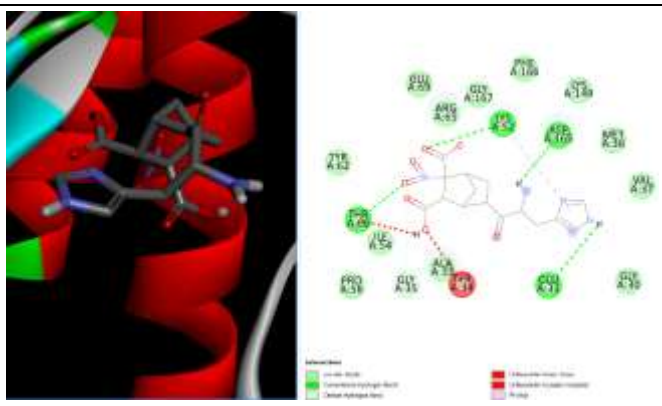
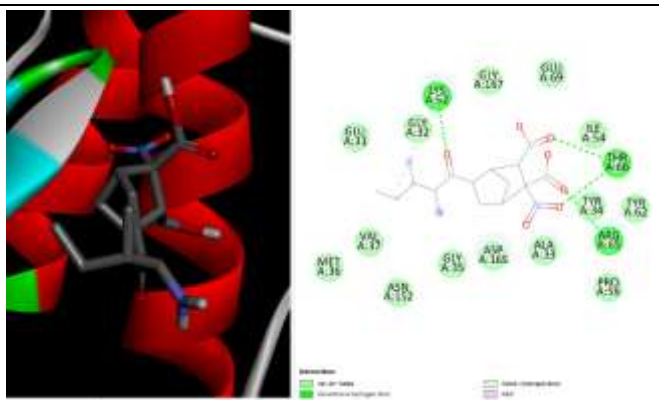
Docking Results of Humic Acid

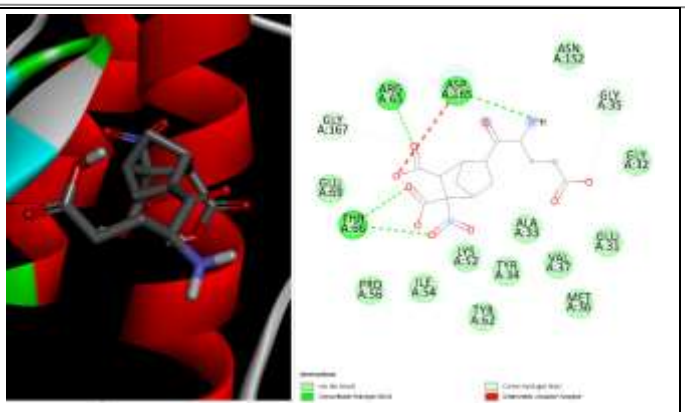
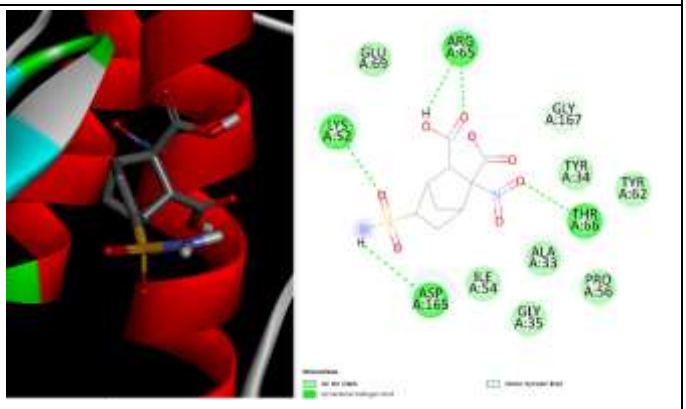
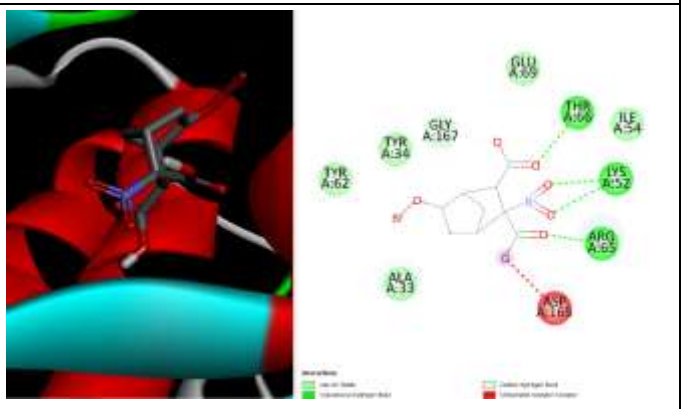
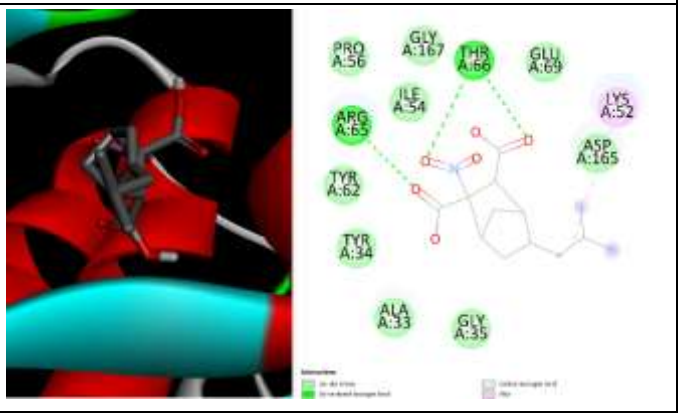
MOLECULE	Binding Affinity	VISUALIZATION
E15	-8.3	
A1	-7.3	
A4	-7.3	
C3	-7.2	

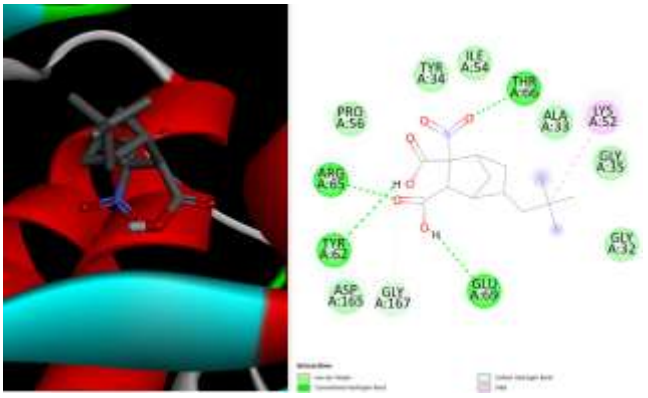
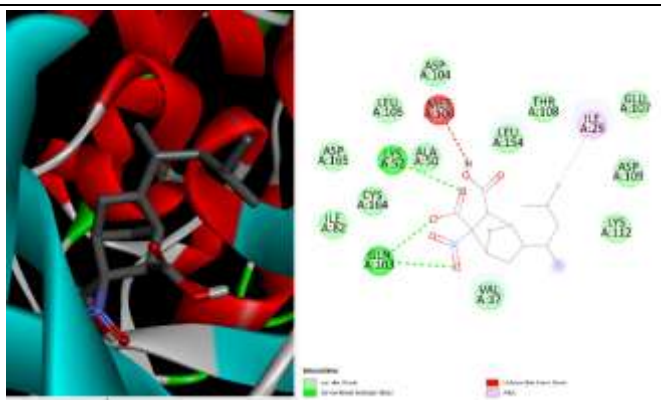
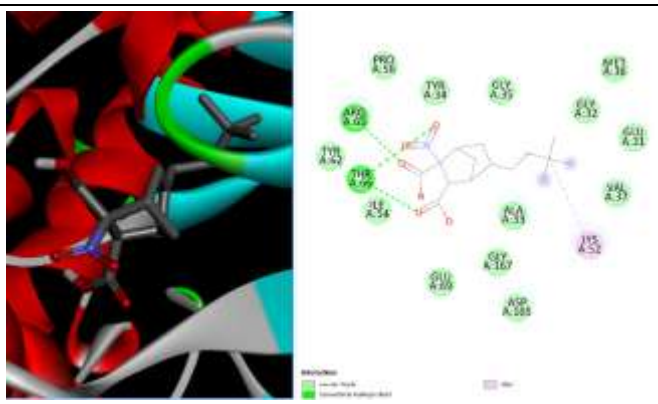
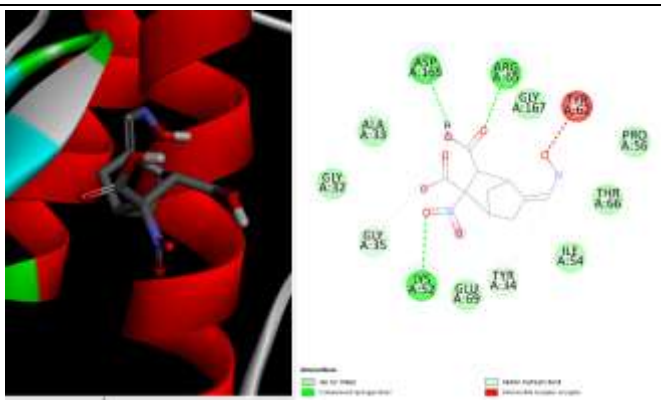
D19	-7.2	
D23	-7.2	
E4	-7.2	
E6	-7.2	

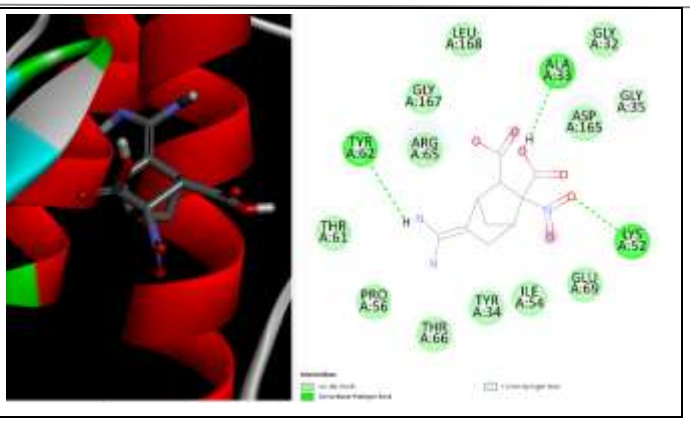
E10	-7.2	
E16	-7.2	
E18	-7.2	
I8	-7.2	

A0	-7.1	
C11	-7.1	
C12	-7.1	
D22	-7.1	

D25	-7.1	
E3	-7.1	
E5	-7.1	
E8	-7.1	

E19	-7.1	
I6	-7.1	
B3	-7	
D6	-7	

D14	-7	
D20	-7	
D24	-7	
I9	-7	

I10	-7	

Physicochemical prediction of Fulvic Acid

MOLECULE	Mol.Formula	Mol.Wt.	Heavy-atoms	Aromatic heavy-atoms	Fraction- Csp3	Rotatable-bonds	H-bond acceptors	H-bond donors	Mol.Ref.	TPSA
E15	C25H22N2O9	494.45	36	19	0.24	5	10	6	127	196
C2	C15H12F2O8	358.25	25	10	0.33	2	10	4	78.3	137
D23	C20H24O8	392.4	28	10	0.5	3	8	4	102	137
D15	C19H22O8	378.37	27	10	0.47	3	8	4	97.3	137
E5	C20H19N3O9	445.38	32	15	0.3	5	11	6	108	209
J1	C14H13NO10S	387.32	26	10	0.29	2	11	5	84.2	206
N1	C15H13NO9	351.27	25	10	0.27	2	9	5	81.3	181
C3	C15H11F3O8	376.24	26	10	0.33	2	11	4	78.2	137
D4	C17H18O8	350.32	25	10	0.41	2	8	4	87.8	137
D8	C18H20O8	364.35	26	10	0.44	2	8	4	92.5	137
D14	C19H22O8	378.37	27	10	0.47	3	8	4	97.1	137
E3	C23H21NO9	455.41	33	16	0.26	5	10	5	115	181
E6	C19H19NO9	405.36	29	10	0.42	3	10	5	102	167
E10	C18H17NO11	423.33	30	10	0.33	5	12	6	97.5	218
I1	C15H11NO8	333.25	24	10	0.27	1	9	4	77.9	161
L2	C15H11FO9	354.24	25	10	0.27	2	10	4	78.6	155
C5	C15H12Cl2O8	391.16	25	10	0.33	2	8	4	87.8	137

C6	C15H11Cl3O8	425.6	26	10	0.33	2	8	4	92.4	137
D5	C18H20O8	364.35	26	10	0.44	4	8	4	92.6	137
E18	C23H21NO10	471.41	34	16	0.26	5	11	6	117	201
G1	C16H14O10	366.28	26	10	0.31	3	10	4	84.5	164
G4	C18H18O10	394.33	28	10	0.39	4	10	4	94.1	164
J2	C14H11ClO10S	406.75	26	10	0.29	2	10	4	86.3	180
K1	C16H14O9	350.28	25	10	0.31	2	9	4	83.4	155
K2	C17H16O9	364.3	26	10	0.35	3	9	4	88.2	155
L1	C15H11ClO9	370.7	25	10	0.27	2	9	4	83.4	155
N4	C15H15N3O8	365.29	26	10	0.27	3	9	7	88.8	199

Physicochemical prediction of Humic Acid

MOLECULE	Mol.Formula	Mol.Wt.	Heavy-atoms	Aromatic heavy-atoms	Fraction-Csp3	Rotatable-bonds	H-bond acceptors	H-bond donors	Mol.Ref.	TPSA
E15	C20H19N3O7	413.38	30	9	0.35	7	8	4	106.03	179.3
A1	C9H8FNO6	245.16	17	0	0.56	3	7	2	52.41	120.42
A4	C9H8INO6	353.07	17	0	0.56	3	6	2	65.32	120.42
C3	C10H8F3NO6	295.17	20	0	0.6	4	9	2	57.36	120.42
D19	C15H21NO6	311.33	22	0	0.73	7	6	2	81.2	120.42
D23	C15H21NO6	311.33	22	0	0.73	5	6	2	80.94	120.42
E4	C15H21N5O7	383.36	27	0	0.6	10	9	6	93.21	225.41
E6	C14H16N2O7	324.29	23	0	0.64	5	8	3	81.2	149.52
E10	C13H14N2O9	342.26	24	0	0.54	7	10	4	76.27	200.81
E16	C14H17N3O8	355.3	25	0	0.57	8	9	4	82.21	206.6
E18	C18H18N2	390.34	28	6	0.39	7	9	4	96.2	183.7

	O8									4
I8	C9H10N2O7	258.18	18	0	0.56	4	7	4	55.89	152.68
A0	C9H9NO6	227.17	16	0	0.56	3	6	2	52.36	120.42
C11	C10H9I2NO6	492.99	19	0	0.6	4	6	2	83.09	120.42
C12	C10H8I3NO6	618.89	20	0	0.6	4	6	2	96.1	120.42
D22	C15H21NO6	311.33	22	0	0.73	7	6	2	81.2	120.42
D25	C15H21NO6	311.33	22	0	0.73	5	6	2	80.94	120.42
E3	C18H18N2O7	374.34	27	6	0.39	7	8	3	94.18	163.51
E5	C15H16N4O7	364.31	26	5	0.47	7	9	4	86.32	192.19
E8	C15H20N2O7	340.33	24	0	0.67	7	8	3	84.11	163.51
E19	C14H16N2O9	356.28	25	0	0.57	8	10	4	81.08	200.81
I6	C9H10N2O8S	306.25	20	0	0.56	4	9	3	64.03	188.96
B3	C9H8BrNO7	322.07	18	0	0.56	4	7	2	61.32	129.65
D6	C13H17NO6	283.28	20	0	0.69	5	6	2	71.59	120.42
D14	C14H19NO6	297.3	21	0	0.71	5	6	2	76.14	120.42

Pharmacokinetic Evaluation of Fulvic Acid

MOLECULE	Formula	GI - absorption	BBB - permeant	Pgp - substrate	CYP1A2 - inhibitor	CYP2C19 - inhibitor	CYP2C9 - inhibitor	CYP2D6- inhibitor	CYP3A4 - inhibitor	Log(Kp) (cm/s)
E15	C25H22N2O9	↓	☒	☒	☒	☒	☒	☒	☒	-9.71
C2	C15H12F2O8	↑	☒	☑	☒	☒	☒	☒	☒	-7.85
D23	C20H24O8	↑	☒	☑	☒	☒	☒	☒	☒	-6.74
D15	C19H22O8	↑	☒	☑	☒	☒	☒	☒	☒	-6.84

E5	C20H19N3O9	↓	☒	☒	☒	☒	☒	☒	☒	-10.8
J1	C14H13N10S	↓	☒	☒	☒	☒	☒	☒	☒	-9.09
N1	C15H13N9	↓	☒	☒	☒	☒	☒	☒	☒	-8.65
C3	C15H11F3O8	↓	☒	☑	☒	☒	☒	☒	☒	-7.77
D4	C17H18O8	↑	☒	☑	☒	☒	☒	☒	☒	-7.44
D8	C18H20O8	↑	☒	☑	☒	☒	☒	☒	☒	-7.14
D14	C19H22O8	↑	☒	☑	☒	☒	☒	☒	☒	-7
E3	C23H21N9	↓	☒	☒	☒	☒	☒	☒	☒	-9.56
E6	C19H19N9	↓	☒	☒	☒	☒	☒	☒	☒	-9.94
E10	C18H17N11	↓	☒	☒	☒	☒	☒	☒	☒	-11.1
I1	C15H11N8	↓	☒	☒	☒	☒	☒	☒	☒	-7.94
L2	C15H11FO9	↓	☒	☒	☒	☒	☒	☒	☒	-7.89
C5	C15H12Cl2O8	↑	☒	☑	☒	☒	☒	☒	☒	-7.7
C6	C15H11Cl3O8	↑	☒	☑	☒	☒	☒	☒	☒	-7.55
D5	C18H20O8	↑	☒	☑	☒	☒	☒	☒	☒	-6.99
E18	C23H21N10	↓	☒	☒	☒	☒	☒	☒	☒	-9.91
G1	C16H14O10	↓	☒	☑	☒	☒	☒	☒	☒	-8.05
G4	C18H18O10	↓	☒	☑	☒	☒	☒	☒	☒	-7.65
J2	C14H11ClO10S	↓	☒	☑	☒	☒	☒	☒	☒	-8.18
K1	C16H14O9	↓	☒	☒	☒	☒	☒	☒	☒	-8.07
K2	C17H16O9	↓	☒	☑	☒	☒	☒	☒	☒	-7.82
L1	C15H11ClO9	↓	☒	☒	☒	☒	☒	☒	☒	-7.61
N4	C15H15N3O8	↓	☒	☒	☒	☒	☒	☒	☒	-9.26

NOTE: ↑: High; **↓:** Low; **☑:** Yes; **☒:** No

Pharmacokinetic Evaluation of Humic Acid

MOLECULE	GI - absorption	BBB - permeant	Pgp - substrate	CYP1A2 - inhibitor	CYP2C19 - inhibitor	CYP2C9 - inhibitor	CYP2D6- inhibitor	CYP3A4- inhibitor	Log(Kp) (cm/s)

E15	↓	☒	☒	☒	☒	☒	☒	☒	-9.97
A1	↑	☒	☒	☒	☒	☒	☒	☒	-7.89
A4	↑	☒	☒	☒	☒	☒	☒	☒	-8.28
C3	↑	☒	☒	☒	☒	☒	☒	☒	-7.76
D19	↑	☒	☒	☒	☒	☒	☒	☒	-6.59
D23	↑	☒	☒	☒	☒	☒	☒	☒	-6.74
E4	↓	☒	☒	☒	☒	☒	☒	☒	-11.59
E6	↓	☒	☒	☒	☒	☒	☒	☒	-10.2
E10	↓	☒	☒	☒	☒	☒	☒	☒	-11.38
E16	↓	☒	☒	☒	☒	☒	☒	☒	-11.66
E18	↓	☒	☒	☒	☒	☒	☒	☒	-10.18
I8	↓	☒	☑	☒	☒	☒	☒	☒	-8.4
A0	↑	☒	☒	☒	☒	☒	☒	☒	-7.65
C11	↑	☒	☒	☒	☒	☒	☒	☒	-8.5
C12	↑	☒	☒	☒	☒	☒	☒	☒	-8.73
D22	↑	☒	☒	☒	☒	☒	☒	☒	-6.59
D25	↑	☒	☑	☒	☒	☒	☒	☒	-6.84
E3	↓	☒	☒	☒	☒	☒	☒	☒	-9.83
E5	↓	☒	☒	☒	☒	☒	☒	☒	-11.06
E8	↓	☒	☑	☒	☒	☒	☒	☒	-9.81
E19	↓	☒	☒	☒	☒	☒	☒	☒	-11.21
I6	↓	☒	☑	☒	☒	☒	☒	☒	-9.35
B3	↑	☒	☒	☒	☒	☒	☒	☒	-7.77
D6	↑	☒	☒	☒	☒	☒	☒	☒	-7.18
D14	↑	☒	☒	☒	☒	☒	☒	☒	-6.99

NOTE: ↑: High; **↓:** Low; **☑:** Yes; **☒:** No

Drug Likeliness Prediction of Fulvic Acid

MOLECULE	Formula	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score
E15	C25H22N2O9	2	1	1	1	2	0.17
C2	C15H12F2O8	0	0	0	1	0	0.56

D23	C20H24O8	0	0	0	1	0	0.56
D15	C19H22O8	0	0	0	1	0	0.56
E5	C20H19N3O9	2	0	1	1	4	0.17
J1	C14H13NO10S	1	0	1	1	2	0.11
N1	C15H13NO9	0	0	1	1	1	0.11
C3	C15H11F3O8	0	0	0	1	1	0.56
D4	C17H18O8	0	0	0	1	0	0.56
D8	C18H20O8	0	0	0	1	0	0.56
D14	C19H22O8	0	0	0	1	0	0.56
E3	C23H21NO9	0	0	1	1	1	0.55
E6	C19H19NO9	0	0	1	1	1	0.55
E10	C18H17NO11	2	1	1	1	4	0.11
I1	C15H11NO8	0	0	1	1	1	0.11
L2	C15H11FO9	0	0	1	1	1	0.11
C5	C15H12Cl2O8	0	0	0	1	0	0.56
C6	C15H11Cl3O8	0	0	0	1	0	0.56
D5	C18H20O8	0	0	0	1	0	0.56
E18	C23H21NO10	2	0	1	1	3	0.17
G1	C16H14O10	0	0	1	1	1	0.11
G4	C18H18O10	0	0	1	1	1	0.11
J2	C14H11ClO10S	0	0	1	1	1	0.11
K1	C16H14O9	0	0	1	1	1	0.11
K2	C17H16O9	0	0	1	1	1	0.11
L1	C15H11ClO9	0	0	1	1	1	0.11
N4	C15H15N3O8	2	0	1	1	2	0.17

Drug Likeliness Prediction of Humic Acid

MOLECULE	Lipinski_violations	Ghose_violations	Veber_violations	Egan_violations	Muegge_violations	Bioavailability Score
E15	0	0	1	1	1	0.11
A1	0	0	0	0	0	0.56
A4	0	0	0	0	0	0.56
C3	0	0	0	0	0	0.56

D19	0	0	0	0	0	0.56
D23	0	0	0	0	0	0.56
E4	2	1	1	1	3	0.17
E6	0	1	1	1	1	0.56
E10	1	1	1	1	2	0.11
E16	1	1	1	1	2	0.11
E18	0	0	1	1	2	0.11
I8	0	1	1	1	1	0.11
A0	0	0	0	0	0	0.56
C11	0	1	0	0	0	0.56
C12	1	1	0	0	1	0.56
D22	0	0	0	0	0	0.56
D25	0	0	0	0	0	0.56
E3	0	0	1	1	1	0.11
E5	1	1	1	1	2	0.55
E8	0	0	1	1	2	0.11
E19	1	1	1	1	2	0.11
I6	0	0	1	1	1	0.11
B3	0	0	0	0	0	0.56
D6	0	0	0	0	0	0.56
D14	0	0	0	0	0	0.56

Toxicity Prediction of Fulvic Acid

MOLECULE	Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
E15	☒	☒	☑	☑	☒	☒	☒	☒	☒
	73	52	56	87	57	68	96	54	59
C2	☒	☒	☑	☑	☒	☒	☒	☒	☒
	75	86	60	74	60	63	99	53	61
D23	☒	☒	☑	☑	☒	☒	☒	☒	☒
	80	84	51	62	55	67	95	53	78
D15	☒	☒	☑	☑	☒	☒	☒	☑	☒
	81	84	57	60	51	70	99	51	78

E5	☒	☑	☑	☑	☒	☒	☒	☒	☒
	72	50	54	86	59	65	99	57	63
J1	☒	☒	☑	☑	☒	☒	☒	☒	☒
	59	79	58	76	58	63	99	59	69
N1	☒	☒	☑	☑	☒	☒	☒	☒	☒
	73	55	62	83	59	61	99	61	53
C3	☒	☒	☑	☑	☒	☒	☒	☒	☒
	76	83	60	74	59	64	97	53	61
D4	☒	☒	☑	☑	☒	☒	☒	☒	☒
	81	85	57	64	54	68	99	53	77
D8	☒	☒	☑	☑	☒	☒	☒	☒	☒
	80	84	51	62	55	67	98	53	78
D14	☒	☒	☑	☑	☒	☒	☒	☑	☒
	83	85	55	60	50	70	99	50	78
E3	☒	☒	☑	☑	☒	☒	☒	☒	☑
	78	52	58	88	57	69	99	50	52
E6	☒	☒	☑	☑	☒	☒	☒	☒	☒
	86	53	57	81	52	64	99	53	61
E10	☒	☒	☑	☑	☒	☒	☒	☒	☑
	75	50	61	88	57	69	99	50	53
I1	☒	☒	☑	☑	☒	☒	☒	☒	☒
	78	74	60	75	62	68	99	53	66
L2	☒	☒	☑	☑	☒	☒	☒	☒	☒
	75	86	60	74	60	63	98	53	61
C5	☒	☒	☑	☑	☒	☒	☒	☒	☒
	76	86	60	72	59	63	99	54	62
C6	☒	☒	☑	☑	☒	☒	☒	☒	☒
	76	84	60	71	58	63	99	54	62
D5	☒	☒	☑	☑	☑	☒	☒	☒	☒
	84	86	62	62	59	75	99	61	72
E18	☒	☒	☑	☑	☒	☒	☒	☒	☑
	78	52	58	88	57	69	99	5	52
G1	☒	☒	☑	☑	☑	☒	☒	☒	☒
	83	82	64	70	59	74	98	54	73

G4	☒	☒	☑	☑	☑	☒	☒	☒	☒
	82	84	62	63	59	70	99	55	75
J2	☒	☒	☑	☑	☒	☒	☒	☒	☒
	59	87	57	61	55	74	99	58	67
K1	☒	☒	☑	☑	☒	☒	☒	☒	☒
	82	86	57	69	58	69	99	53	74
K2	☒	☒	☑	☑	☒	☒	☒	☒	☒
	84	86	62	67	54	77	99	51	74
L1	☒	☒	☑	☑	☒	☒	☒	☒	☒
	76	86	60	72	59	63	98	54	62
N4	☒	☒	☑	☑	☒	☒	☒	☑	☒
	69	50	65	82	56	58	99	50	59

***All values are in %age Probablity**

NOTE:- ☑: Active ; **☒:** Inactive

Toxicity Prediction of Humic Acid

MOLECULE	Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
E15	☒	☒	☑	☑	☑	☒	☒	☒	☒
	83	84	64	65	51	75	99	53	76
ACT1	☒	☒	☑	☑	☒	☒	☒	☒	☒
	76	83	60	72	59	60	97	52	61
ACT4	☒	☒	☑	☑	☒	☒	☒	☒	☒
	77	85	62	72	59	63	97	52	64
C3	☒	☒	☑	☑	☑	☒	☒	☒	☒
	83	84	64	65	51	75	99	53	76
D19	☒	☒	☑	☑	☑	☒	☒	☒	☒
	84	86	62	62	59	75	99	61	72
D23	☒	☒	☑	☑	☒	☒	☒	☒	☒
	83	87	56	71	61	67	99	52	73
E4	☒	☒	☑	☑	☒	☒	☒	☑	☒
	75	85	62	70	50	66	98	50	65
E6	☒	☒	☑	☑	☒	☒	☒	☑	☒
	75	87	63	70	50	69	99	51	68

E18	☒	☒	☑	☑	☑	☒	☒	☒	☒
	84	86	60	57	63	68	99	59	72
I8	☒	☒	☑	☑	☒	☒	☒	☒	☒
	82	87	61	70	50	69	99	53	65
ACT0	☒	☒	☑	☑	☒	☒	☒	☒	☒
	76	85	60	73	60	60	99	53	60
C11	☒	☒	☑	☑	☑	☒	☒	☒	☒
	75	87	62	70	50	69	99	50	66
C12	☒	☒	☑	☑	☒	☒	☒	☑	☒
	75	85	62	70	50	66	98	50	65
D22	☒	☒	☑	☑	☒	☒	☒	☒	☒
	82	87	61	70	50	69	99	53	65
D25	☒	☒	☑	☑	☒	☒	☒	☒	☒
	73	86	64	71	59	62	99	54	58
E3	☒	☒	☑	☑	☑	☒	☒	☒	☒
	75	87	62	70	50	69	99	50	66
E5	☒	☒	☑	☒	☒	☒	☒	☑	☒
	74	86	62	71	50	70	99	50	66
E8	☒	☒	☑	☑	☒	☒	☒	☒	☒
	77	85	62	72	59	63	97	52	64
E19	☒	☒	☑	☑	☑	☒	☒	☒	☒
	84	85	64	60	63	72	99	62	74
I6	☒	☒	☑	☑	☒	☒	☒	☒	☒
	75	86	60	74	60	63	99	53	61
B3	☒	☒	☑	☑	☑	☒	☒	☒	☒
	84	86	62	62	59	75	99	61	72
D6	☒	☒	☑	☑	☒	☒	☒	☒	☒
	76	83	60	74	59	64	97	53	61
D14	☒	☒	☑	☑	☑	☒	☒	☒	☒
	83	82	64	70	59	74	98	54	73

***All values are in %age Probablity**

NOTE:- ☑: Active ; **☒:** Inactive

Adverse Drug Reaction Prediction of Fulvic Acid

E15	Pa	Pi	Side effect	E10	Pa	Pi	Side effect
	0.348	0.118	Myocardial infarction		0.453	0.222	Hepato-toxicity
C2	Pa	Pi	Side effect		0.273	0.186	Nephro-toxicity
	0.624	0.132	Hepato-toxicity	I1	Pa	Pi	Side effect
	0.367	0.104	Nephro-toxicity		0.315	0.141	Nephro-toxicity
D23	Pa	Pi	Side effect	L2	Pa	Pi	Side effect
	0.5	0.195	Hepato-toxicity		0.624	0.132	Hepato-toxicity
	0.307	0.149	Nephro-toxicity		0.367	0.104	Nephro-toxicity
D15	Pa	Pi	Side effect	C5	Pa	Pi	Side effect
	0.684	0.106	Hepato-toxicity		0.453	0.222	Hepato-toxicity
	0.413	0.079	Nephro-toxicity		0.311	0.145	Nephro-toxicity
E5	Pa	Pi	Side effect	C6	Pa	Pi	Side effect
	0.571	0.159	Hepato-toxicity		0.584	0.152	Hepato-toxicity
	0.284	0.175	Nephro-toxicity		0.349	0.115	Nephro-toxicity
J1	Pa	Pi	Side effect	D5	Pa	Pi	Side effect
	0.377	0.115	Cardiac failure		0.628	0.13	Hepato-toxicity
	0.278	0.254	Myocardial infarction		0.376	0.098	Nephro-toxicity
N1	Pa	Pi	Side effect	E18	NO DATA AVAILABLE		
	0.585	0.152	Hepato-toxicity	G1	Pa	Pi	Side effect
	0.277	0.182	Nephro-toxicity		0.305	0.152	Nephro-toxicity
C3	Pa	Pi	Side effect	G4	Pa	Pi	Side effect
	0.716	0.094	Hepato-toxicity		0.375	0.099	Nephro-toxicity
	0.336	0.124	Nephro-toxicity	J2	Pa	Pi	Side effect
D4	Pa	Pi	Side effect		0.615	0.136	Hepato-toxicity
	0.586	0.151	Hepato-toxicity		0.333	0.126	Nephro-toxicity
	0.382	0.095	Nephro-toxicity		0.24	0.232	Cardiac failure
D8	Pa	Pi	Side effect	K1	Pa	Pi	Side effect
	0.5	0.195	Hepato-toxicity		0.476	0.068	Cardiac failure
	0.307	0.149	Nephro-toxicity		0.379	0.274	Hepato-toxicity
D14	Pa	Pi	Side effect		0.294	0.163	Nephro-toxicity
	0.684	0.106	Hepato-toxicity	K2	Pa	Pi	Side effect
	0.413	0.079	Nephro-toxicity		0.635	0.127	Hepato-toxicity
E3	Pa	Pi	Side effect		0.312	0.144	Nephro-toxicity
	0.571	0.159	Hepato-toxicity	L1	Pa	Pi	Side effect

	0.284	0.175	Nephro-toxicity		0.584	0.152	Hepato-toxicity
E6	Pa	Pi	Side effect		0.349	0.115	Nephro-toxicity
	0.571	0.159	Hepato-toxicity	N4	Pa	Pi	Side effect
	0.284	0.175	Nephro-toxicity		0.6	0.144	Hepato-toxicity

Adverse Drug Reaction Prediction of Humic Acid

E15	Pa	Pi	Side effect	A0	Pa	Pi	Side effect
	0.571	0.159	Hepato-toxicity		0.273	0.264	Myocardial infarction
	0.284	0.175	Nephro-toxicity	C11	Pa	Pi	Side effect
A1	Pa	Pi	Side effect		0.571	0.159	Hepato-toxicity
	0.637	0.126	Hepato-toxicity		0.284	0.175	Nephro-toxicity
	0.318	0.139	Nephro-toxicity	C12	Pa	Pi	Side effect
A4	Pa	Pi	Side effect		0.571	0.159	Hepato-toxicity
	0.684	0.106	Hepato-toxicity		0.284	0.175	Nephro-toxicity
	0.413	0.079	Nephro-toxicity	D22	Pa	Pi	Side effect
C3	Pa	Pi	Side effect		0.584	0.152	Hepato-toxicity
	0.695	0.102	Hepato-toxicity		0.349	0.115	Nephro-toxicity
	0.349	0.115	Nephro-toxicity	D25	Pa	Pi	Side effect
	0.324	0.149	Cardiac failure		0.637	0.126	Hepato-toxicity
	0.31	0.179	Myocardial infarction		0.318	0.139	Nephro-toxicity
D19	Pa	Pi	Side effect	E3	Pa	Pi	Side effect
	0.716	0.094	Hepato-toxicity		0.684	0.106	Hepato-toxicity
	0.336	0.124	Nephro-toxicity		0.413	0.079	Nephro-toxicity
D23	Pa	Pi	Side effect	E5	Pa	Pi	Side effect
	0.637	0.126	Hepato-toxicity		0.436	0.233	Hepato-toxicity
	0.318	0.139	Nephro-toxicity		0.348	0.116	Nephro-toxicity
E4	Pa	Pi	Side effect	E8	Pa	Pi	Side effect
	0.365	0.105	Nephro-toxicity		0.628	0.13	Hepato-toxicity
E6	Pa	Pi	Side effect		0.376	0.098	Nephro-toxicity
	0.586	0.151	Hepato-toxicity	E19	Pa	Pi	Side effect
	0.382	0.095	Nephro-toxicity		0.716	0.094	Hepato-toxicity
E10	Pa	Pi	Side effect		0.336	0.124	Nephro-toxicity
	0.659	0.117	Hepato-toxicity	I6	Pa	Pi	Side effect
	0.405	0.083	Nephro-toxicity		0.453	0.222	Hepato-toxicity
E16	Pa	Pi	Side effect		0.273	0.186	Nephro-toxicity

	0.571	0.159	Hepato-toxicity		Pa	Pi	Side effect
	0.284	0.175	Nephro-toxicity	B3	0.436	0.233	Hepato-toxicity
	Pa	Pi	Side effect		0.348	0.116	Nephro-toxicity
E18	0.624	0.132	Hepato-toxicity		Pa	Pi	Side effect
	0.367	0.104	Nephro-toxicity	D6	0.453	0.222	Hepato-toxicity
	Pa	Pi	Side effect		0.311	0.145	Nephro-toxicity
I8	0.584	0.152	Hepato-toxicity		Pa	Pi	Side effect
	0.349	0.115	Nephro-toxicity	D14	0.571	0.159	Hepato-toxicity
					0.284	0.175	Nephro-toxicity

4. DISCUSSION

The study explored the potential of novel humic acid and fulvic acid derivatives as antidiabetic agents through a comprehensive computer-aided drug design (CADD) approach, encompassing molecular design, docking simulations, pharmacokinetics, toxicity predictions, and in-silico biological activity evaluations.

• Design and Docking:

The initial design of the derivatives incorporated functional groups such as hydroxyl, carboxyl, and methoxy, which are known to enhance molecular interactions with diabetic targets. Docking studies revealed that several compounds showed strong binding affinities to key targets suggesting that these derivatives could potentially act as antidiabetic agents.

• Pharmacokinetics (ADME):

The predicted pharmacokinetic profiles indicated that the compounds have favourable characteristics for oral bioavailability, suitable absorption, and low metabolic clearance, which are important for effective drug delivery. The results suggest that these compounds could be easily absorbed and have prolonged action in the body, making them strong candidates for further optimization in terms of bioavailability and half-life.

• Toxicity Predictions:

Toxicity assessments showed that most of the derivatives exhibited low predicted toxicity, suggesting that they may be safe for use in the long-term management of diabetes. However, these predictions are based on computational models, and experimental validation is required to confirm the safety profile.

• Biological Activity Predictions:

In-silico biological activity predictions indicated that the derivatives might act through multiple mechanisms, including inhibition of α-glucosidase, modulation of insulin sensitivity, and reduction of oxidative stress—critical pathways in diabetes. These findings are consistent with existing literature on the beneficial effects of humic and fulvic acids in metabolic disorders, suggesting that these derivatives could offer new therapeutic avenues for diabetes treatment.

5. CONCLUSION

The study presented in this report focuses on the computational design, docking studies, pharmacokinetics, toxicity prediction, and in-silico biological activity analysis of novel humic acid and fulvic acid derivatives as potential antidiabetic agents. Through an integrated approach involving computer-aided drug design (CADD), we identified promising derivatives with favourable binding affinities to key diabetic target(Extracellular Signal-regulated Kinase 2 (ERK2) .

The docking studies demonstrated that several derivatives exhibited strong interactions with the active sites of these targets, suggesting their potential as effective antidiabetic agents. Furthermore, pharmacokinetic analysis indicated that the most promising compounds have desirable properties, such as good oral bioavailability, suitable absorption, and low metabolic clearance, which are critical for their development as therapeutic agents. Toxicity predictions also showed that the selected derivatives have a relatively low risk of adverse effects, making them safe candidates for further experimental validation.

In-silico biological activity predictions supported the potential efficacy of these compounds, highlighting their ability to modulate key biological pathways involved in diabetes. This comprehensive computational approach provides a solid foundation for the synthesis and in-vitro evaluation of humic acid and fulvic acid derivatives as potential antidiabetic agents.

Overall, the findings of this report suggest that humic acid and fulvic acid derivatives, when optimized through further

computational studies and experimental validation, could offer a novel and promising class of compounds for the treatment of diabetes, contributing to the ongoing search for safer and more effective antidiabetic therapies.

REFERENCES

[1] "Abd Al-Rahman S Al-Shudiefat1*, Jihad A. M. Alzyoud2, Review: Shilajit (Mumie) A natural Product with Anti-hyperglycemic, Anti-obesity, Antioxidant, and Anti-Inflammatory properties for a potential treatment of diabetes mellitus, Volume 17, Number 1, March 2024, ISSN 1995-6673, Pages 109 – 122."

[2] "A. Osama, humic and fulvic acids alleviate oxidative damage induced by hydrogen peroxide, environ. Sci 8 (4), 555-580, 2013"

[3] "Himalayan Medicinal Resources: Present and Future. A Case Study: Antidiabetic Activity of Shilajit, Purusotam Basnet Plant Resources 4 (3), 161-170, 2001"

[4] "Evaluation of Alpha-amylase and Alpha-glucosidase Inhibitory activities of Shilajit Anuya Aparna Anil Rege, Abhay Sadashiv Chowdhary International Journal of Advanced Research 2 (2), 735-40, 2014"

[5] "Fulvic acid attenuates homocysteine-induced cyclooxygenase-2 expression in human monocytes, Shao-Ju Chien, Te-Chuan Chen, Hsing-Chun Kuo, Cheng-Nan Chen, Shun-Fu Chang, BMC Complementary and Alternative Medicine 15, 1-8, 2015"

[6] "Winkler J, Ghosh S. Therapeutic Potential of Fulvic Acid in Chronic Inflammatory Diseases and Diabetes. J Diabetes Res. 2018 Sep 10;2018:5391014."

[7] "Aronov, A. M.; Baker, C.; Bemis, G. W.; Cao, J.; Chen, G.; Ford, P. J.; Germann, U. A.; Green, J.; Hale, M. R.; Jacobs, M.; Janetka, J. W.; Maltais, F.; Martinez-Botella, G.; Namchuk, M. N.; Straub, J.; Tang, Q.; Xie, X. Flipped Out: Structure-Guided Design of Selective Pyrazolylpyrrole ERK Inhibitors. J. Med. Chem. 2007, 50(6), 1280–1287."

[8] Https://www.acdlabs.com/

[9] Http://www.swissadme.ch/

[10] Http://www.way2drug.com/adverpred/index.php

[11] Https://www.rcsb.org/

[12] Https://pyrx.sourceforge.io/

[13] Https://pymol.org/2/

[14] Https://discover.3ds.com/discovery-studio-visualizer-download

[15] Https://tox-new.charite.de/protox_II/index.php?Site=compound_input.